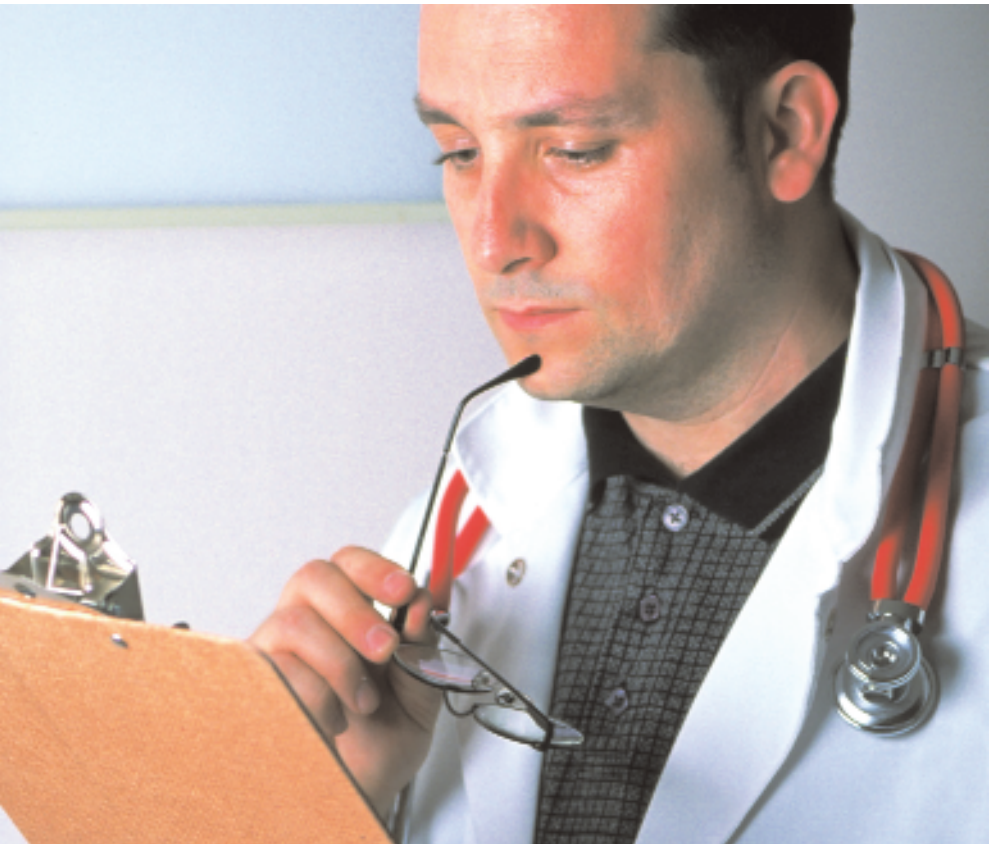
Update on Cognition



COGNITIVE OUTCOMES IN THE CATIE SCHIZOPHRENIA TRIAL:

Why do they seem different from previous results?

by Philip D. Harvey, PhD

The CATIE trial was designed to evaluate the differential benefits of newer antipsychotic medications and compare them to the benefits of conventional antipsychotic treatments. This trial was designed to be a definitive effectiveness study, examining the whole host of potential outcomes, starting with all-cause discontinuation, clinical response, cognition, and a variety of other outcomes, including cost effectiveness and longer-term side effects. Although the study was designed to be definitive, a number of questions have arisen about the study and whether the study, despite its large sample size and broad inclusion criteria, provides a representative assessment of effects of antipsychotic medications in typical patients with schizophrenia. Addressing many of these issues is outside the scope of a column on cognition. There are, however, several features of the research design and patient populations studied that are quite germane to the cognitive results and their attendant implications for functional outcomes associated with antipsychotic treatments.

The CATIE cognition results. In brief, the CATIE cognition component included a comprehensive cognitive assessment[1] that was performed at baseline prior to randomization to their initial treatment with risperidone, olanzapine, quetiapine, or the conventional antipsychotic perphenazine. Ziprasidone treatment was added after the study was designed and resulted in a smaller sample size. Reassessment was performed at six months for patients who were still receiving the same treatment (n=523) and at 18 months (n=303). Thus, 21 percent of the patients who were in the trial were still on the same medication at 18 months and about 33 percent of the patients who were re-evaluated at two months were still on the same treatment 16 months later.

The basic results are simple to describe.[2] Changes for each treatment at each endpoint reflected statistically significant improvements from the baseline score. There were no differences between treatments at the two- and six-month endpoints. The average improvements in the cognitive composite score was about 0.25 SD at most. Perphenazine was significantly superior to olanzapine and risperidone at the 18 month

endpoint. Standing doses of benztropine did not worsen cognitive performance, but patients who had benztropine added during the first two months of treatment evidenced worsening in cognitive functioning. Finally, early cognitive improvement predicted remaining on the initial treatments for the entire 18-month period for patients treated with ziprasidone and quetiapine, but not the other treatments.

Where does this differ from previous findings? The reports of high rates of discontinuations early in the CATIE trial attracted substantial media attention. As important was the finding that conventional medications did not appear to be inferior on efficacy measures[3] and appeared superior on cost effectiveness.[4] Multiple previous studies have suggested superiority of atypicals to conventionals for cognitiom,[5] a finding not confirmed in this study. While the amount of improvement seen with atypical treatment was consistent with previous meta-analyses,[5,6] the amount of improvement seen with perphenazine was greater than previous studies of conventional medications. Further, olanzapine and risperidone treatment, both previously shown superior to conventional treatments in head to head trials,[5,6] were found to be inferior at the 18-month endpoint.

What are the reasons for the differences? There are several possible reasons for the differences between these findings and earlier ones. These include the characteristics of the patients in terms of both treatment responsiveness, substance abuse, and chronicity and the dosing of the medications. We will consider these factors in turn.

Treatment responsiveness. The CATIE project included patients whose history of prior treatment response was poor. This may be related to the high rates of discontinuation due to lack of efficacy. At the same time, previous studies of patients with a history of poor treatment response in terms of clinical symptoms have found very reasonable patterns of cognitive response. In specific, Bilder, et al.,[7] found olanzapine and risperidone superior to haloperidol in patients with a history of poor clinical response. There is also evidence to suggest that patients with a particularly robust and rapid clinical response, as well as good adherence to treatment, manifest the most substantial cognitive response[8] to atypical antipsychotic treatment. Thus, treatment resistance may not reduce a modest cognitive benefit, but a different subset of patients may demonstrate the best response.

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Substance abuse. The vast majority of the clinical trials previously examining cognition in schizophrenia and atypical antipsychotic treatments excluded patients with any evidence of substance abuse. The CATIE study intentionally included these patients who may reflect a substantial subset of people with schizophrenia. The inclusion of these participants may affect the results of the study relative to previous studies. There are currently few empirical data on which to base this argument.

Chronicity. Although the patients in the CATIE study were quite chronic, patients in several previous studies where larger beneficial cognitive effects were detected were, if anything, more chronic and more symptomatic.[7,8] However, most studies where chronic patients received substantial benefits from atypicals involved their first exposure to these treatments. Thus, patients with lengthy and often high-dose exposure to conventionals appeared to have a more substantial benefit. In addition, first episode studies have suggested smaller benefits associated with atypical treatments than patients with an established course of illness. We will return to the dosing issue later, but there are additional complexities in this situation.

Most of the studies that were reviewed in previous meta-analyses had a substantial number of patients who were never previously treated with atypicals. Other studies carefully exposed patients to newer medications who had never been exposed to them previously.[9] In the CATIE study, only 10 percent of the patients at baseline were treated with conventional medications, and there is no reason to believe that at least some of them were treated

with atypicals at some point in the past. Twenty-five percent of the CATIE patients were antipsychotic-free, but most had been treated with atypicals in the past. Thus, if there was a unique benefit associated with the class of atypicals in the cognitive domain, many of these patients would have experienced that previously in earlier treatment episodes. It should be kept in mind that most people with schizophrenia, other than first episode patients, will have a treatment history with atypicals and any medications that they are placed on are likely to be far from their first atypical treatment.

Dosing. Dosing of antipsychotics has been complex since the 1950s and the apparent complexity of dosing atypicals is probably because substantial attention has been paid to this issue. However, early comparative studies of conventionals compared to atypical medications typically used doses of the conventionals that conferred an instant benefit to the atypicals. These studies typically reported no benefit to an adverse effect of conventional treatments. Studies with lower doses of atypicals, such as the study reported by Harvey, et al.,[10] found that the relative benefit of atypicals was smaller and that the benefit associated with conventional treatment at very low doses (about 2.5mg/day of haloperidol) was statistically significant.

The CATIE study used a low dose of a conventional medication. There was also substantial variation in the dosing of the atypicals. For instance, the average dose of olanzapine was 20mg/day, which is a relatively high dose, and olanzapine was shown both to have the greatest long-term clinical efficacy and significantly poorer cognitive outcomes than the conventional comparators. In contrast, ziprasidone seemed like it performed the most poorly in terms of efficacy, but its cognitive outcomes seemed quite reasonable from the long-term treatment perspective. A careful examination of ziprasidone dosing, based on the dose range and the average dose presented in the original CATIE paper, indicates that as many as 45 percent of the patients treated with ziprasidone received the lowest possible dose (40mg/day). Thus, a dosing-related dysjunction between clinical and cognitive benefits seems possible.

Previous evidence has suggested that low-dose conventional medications, although showing a smaller relative cognitive disadvantage, may have clinical limitations. Low doses of haloperidol in first-episode patients were associated with greater risk for relapse and development of tardive dyskinesia than were similar doses of risperidone.[11] These data suggest a complicated relationship between cognition, clinical efficacy, relapse, and side effects. The design of the CATIE study, with no true relapse-prevention component, does not allow for a direct test theory that low doses of perphenazine should be associated with relapse risk, particularly compared to high doses of olanzapine.

The take home points. The results of the CATIE study suggest that atypical antipsychotics do not provide a generic benefit on cognition that is superior to conventional treatments. These results do not indicate that there is not potentially a substantial cognitive benefit for a subset of patients with schizophrenia. The results do not address the issue of whether there is a relapse-related

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cost associated with low doses of perphenazine, but at the extreme ends of the dosing spectrum, they do suggest that high doses of antipsychotics, atypicals included, are associated with greater clinical benefits and potential cognitive liabilities. Lower doses were associated, in general, with reduced clinical benefits, and the suggestion that those patients who experienced cognitive improvement with those doses were likely to remain in treatment for the duration of the study.

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AUTHOR NOTE. Dr. Harvey was an author on the CATIE cognition results. His evaluations and comments on the CATIE study do not reflect any official position of the CATIE investigators. No additional analyses of the data beyond those previously performed were performed for this study.

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